SIMCOR® (niacin extended-release/simvastatin)
MEDICAID CLINICAL SUMMARY

Updated April 8, 2008

SIMCOR, a combination of simvastatin, an HMG-CoA reductase inhibitor and niacin extended-release (Niaspan®), is indicated as adjunct to diet for patients requiring modifications of lipid profiles.[1] SIMCOR was approved by the FDA on Feb 15, 2008 and is indicated to reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia when treatment with simvastatin or Niaspan monotherapies are considered inadequate.

SIMCOR is administered as a single daily dose at bedtime, with a low fat snack. The SIMCOR (niacin extended-release/simvastatin) tablet is available in strengths of 500/20 mg, 750/20 mg, and 1000/20 mg. The dosage range is 500/20 mg/day to 2000/40 mg/day with a recommended initial dose of 500/20 mg/day for patients not previously taking niacin extended-release. The dose should be increased based upon desired lipid effects and individual tolerability.

SIMCOR CLINICAL EFFICACY AND SAFETY

SIMCOR reduces non-HDL-C, LDL-C, TC, TG, and Apo B and increases HDL-C in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.[1]

The SEACOAST (The Safety and Efficacy of A COmbination of NiAcin ER and Simvastatin in PaTients With Dyslipidemia) study, a pivotal phase III, double-blind, randomized, multicenter, multi-national, active-controlled, 24 week study, compared the efficacy and safety of SIMCOR with low-dose and high-dose simvastatin in adult patients (N=641) with type II hyperlipidemia or mixed dyslipidemia.[1,2,3] Significantly greater reductions in non-HDL-C levels were observed in subjects treated with SIMCOR 2000/20 mg ($p<0.05$) and SIMCOR 1000/20 mg ($p<0.05$) compared with subjects treated with simvastatin 20 mg. Reductions in non-HDL-C observed in subjects treated with SIMCOR 2000/40 mg and 1000/40 mg were non-inferior to the reduction observed in subjects treated with simvastatin 80 mg.

A separate phase III study, OCEANS (An Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and SimvAstatin in PatieNts with DySlipidemia), was designed to demonstrate long-term (up to 52 weeks) safety of SIMCOR in adult patients (N=520) with primary type II hyperlipidemia or mixed dyslipidemia and to demonstrate the effects of SIMCOR on lipid parameters.[4] Treatment with once-daily SIMCOR 2000/40 mg reduced non-HDL-C, LDL-C, TG, and Lp(a) and increased HDL-C beyond simvastatin 40-mg treated baseline. Moreover, this response was maintained for up to 52 weeks of therapy.

In SEACOAST, flushing occurred in 59% of SIMCOR-treated patients and resulted in study discontinuation for 6% of patients compared to a 0.8% discontinuation rate for simvastatin-treated patients.[1,2,5] Serious adverse events were reported in 0.2% of subjects treated with SIMCOR and 0.8% of subjects treated with simvastatin.[2,5] In OCEANS, at least 1 episode of flushing occurred in approximately 71% of patients, but most episodes observed in the overall population were generally mild in intensity and their incidence decreased over the course of the study.[4] Flushing contributed to discontinuation in 7.1% of patients. Flushing may be reduced in frequency or severity by pretreatment with aspirin or other non-steroidal anti-inflammatory drugs (approximately 30 minutes prior to SIMCOR dose).[1] The observed safety profile of SIMCOR in both studies was consistent with the known safety profiles for each of the individual components.

SIMCOR is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases, active peptic ulcer disease, arterial bleeding; in women who are pregnant or may become pregnant, nursing mothers, and in patients with hypersensitivity to any product ingredient.[1] In clinical studies, there were no

observed cases of myopathy or rhabdomyolysis.[5] However, myopathy and/or rhabdomyolysis have been reported when simvastatin is used in combination with lipid-altering doses (≥1 g/day) of niacin.[1] Patients on SIMCOR should be monitored for muscle pain, tenderness or weakness, particularly during the initial month of treatment or during upward dose titration. In addition to flushing, other common adverse events occurring in ≥3% of patients treated with SIMCOR included headache, pruritus, nausea, back pain, and diarrhea.

No incremental benefit of SIMCOR on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin monotherapy and niacin monotherapy has been established. The safety and efficacy of the individual components of SIMCOR are well established.

NIACIN AND NIACIN EXTENDED-RELEASE
The Coronary Drug Project was a double blind, placebo-controlled secondary prevention study that assessed the safety and efficacy of niacin.[6] Treatment with niacin resulted in a statistically significant reduction in the incidence of nonfatal, recurrent MI. Although a trend toward decreased mortality was not statistically significant, a follow-up at year 15 showed a reduction of 11% in mortality in the niacin treatment group.[7]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol study[8] (ARBITER 2) assessed the effect of adding niacin extended-release to a statin on atherosclerotic progression and cardiovascular events. ARBITER 2 used carotid intima-media thickness (CIMT), a well-established surrogate endpoint for CHD events, as their imaging technique.[9] According to a recent meta-analysis, a 0.1 mm increase in CIMT increases the future risk of MI by 10-15% and stroke by 13-18%.[10] Following a year of therapy in ARBITER 2, the mean CIMT increased significantly in the placebo group (0.044 ± 0.100 mm; $p<0.001$) and was unchanged in the extended-release niacin group (0.014 ± 0.104 mm; $p=0.23$), although the difference between groups was not statistically significant ($p=0.08$).[8]

SIMVASTATIN
In two large, placebo-controlled clinical trials, the Scandinavian Simvastatin Survival Study[11] ([4S], N=4,444 patients) and the Heart Protection Study[12] ([HPS]; N=20,536 patients), the effects of treatment with simvastatin 20-40 mg/day were assessed in patients at high risk of coronary events. Compared to placebo, simvastatin was proven to reduce:

- the risk of total mortality by reducing CHD deaths (4S by 30%, $p=0.0003$[11]; HPS by 13%, $p=0.0003$[12]);
- the risk of non-fatal myocardial infarction (4S by 37%[11]; HPS by 38%, $p<0.0001$[12]) and stroke (4S by 30% for fatal plus nonfatal cerebrovascular events, $p=0.024$[11]; HPS by 25% for stroke, $p<0.0001$[12]);
- the need for coronary (4S by 37%, $p<0.00001$[11]; HPS by 30%, $p<0.0001$[12]) and non-coronary revascularization procedures (HPS by 16% $p=0.006$[12]).

RESIDUAL RISK
Trials using statins to lower LDL cholesterol have consistently shown reductions in major cardiovascular events.[13] In fact, currently available statins, at doses typically used, lower LDL-C levels by 30-40%, which translates into a similar risk reduction in coronary heart disease (CHD) over 5 years.[14] However, despite LDL-lowering, a residual CHD risk remains, some of which may be modifiable. While NCEP ATP III Guidelines[14] have determined that the primary target of treatment for hyperlipidemia is a reduction in LDL-C, they also consider non-HDL-C a secondary target of therapy if triglycerides are high (≥200 mg/dL).[14,15] Non HDL-C is highly correlated with total Apo B the major apolipoprotein of all atherogenic lipoproteins. Non-HDL represents the total cholesterol burden in atherogenic lipoproteins, incuding VLDL and IDL. This combined hyperlipidemia often requires combination therapy.

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SUMMARY

Despite LDL-lowering with statin treatment, a residual CHD risk remains, some of which may be modifiable. Beyond the priority of LDL-C, the NCEP guidelines acknowledge the importance of non-HDL-C.[14,15]

SIMCOR a combination tablet combining a proven simvastatin with a niacin extended-release, is indicated to reduce non-HDL-C, LDL-C, TC, TG, and Apo B and increases HDL-C in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia when treatment with simvastatin or niacin monotherapies are considered inadequate.[1]

REFERENCES

1. SIMCOR® prescribing information, Abbott Laboratories (see http://www.rxabbott.com/pdf/simcor_pi.pdf).
2. Ballantyne CM, Davidson MH, McKenney J, et al. The safety and efficacy of a combination of extended-release niacin and simvastatin in patients with dyslipidemia (SEACOAST): a dose-ranging study. Poster presented at: The 2007 Scientific Sessions of the American Heart Association; November 4-7, 2007; Orlando, FL.
3. Ballantyne CM, Davidson MH, McKenney JM, et al. Comparison of the efficacy and safety of a combination tablet of niacin extended-release and simvastatin with simvastatin 80 mg monotherapy: the SEACOAST II (high-dose) study. *J Clin Lipidology*. 2008;2:79-90.
4. Karas RH, Kashyap ML, Knopp RH, et al. Long-term safety and efficacy of a combination of niacin extended release and simvastatin in patients with dyslipidemia: the OCEANS study. *Am J Cardiovasc Drugs*. 2008;8(2):69-81.
5. Abbott Laboratories, Data on File.
6. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA*. 1975;231(4):360-81.
7. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245-55.
8. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2. *Circulation*. 2004;110:3512-17.
9. Devine PJ, Carlson DW, Taylor AJ. Clinical value of carotid intima-media thickness testing. *J Nucl Cardiol*. 2006;13(5):710-8.
10. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459-67.
11. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet*. 1994:344:1383-89.
12. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin on 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
13. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-78.
14. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP). *Circulation*. 2002;106:3143-21.
15. Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227-39.